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(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940–0874 (US).

(72) Inventors: COMMONS, Thomas, Joseph; 397 Drummers Lane, Wayne, PA 1908 (US). MUSIAL, Christa, L.; 1091 Mill Creek Road, Wycombe, PA 18980 (US). CHRISTMAN, Susan; Unit 8C, 299 Locust Street, Philadelphia, PA 19106 (US).

(74) Agents: ALICE, Ronald, W.; American Home Products Corporation, One Campus Drive, Parsippany, NJ 07054 (US) et al.

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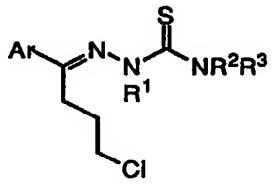

(I)

(57) Abstract

This invention relates to the treatment of atherosclerosis via raising the level of HDL cholesterol by administration of a compound of formula (I), wherein R^1, R^2 and R^3 are independently hydrogen, C_1–C_{10} alkyl, or $-(CH_2)_{0-6}Ar^1$ where Ar^1 is phenyl, furanly, pyridinyl or thienyl, and Ar^1 is optionally substituted by halogen, cyano, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, trifluoromethyl, C_1–C_6 alkoxycarbonyl, $-CO_2H$ or OH.

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ELEVATION OF HDL CHOLESTEROL BY 2-(4-CHLORO-1-ARYL-BUTYLIDENE)-HYDRAZINECARBOTHIOAMIDES

Field of Invention

This invention relates to compounds useful in elevating high density lipoprotein, the "good" cholesterol. Compounds of this invention increase plasma levels of HDL in a cholesterol fed rat model and as such these compounds may be useful for treating diseases such as atherosclerosis.

Background of the Invention

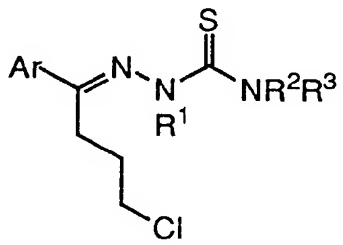
It is widely believed that HDL is a "protective" lipoprotein [Gloria Lena Vega and Scott Grundy, Current Opinion in Lipidology, 7, 209-216 (1996)] and that increasing plasma levels of HDL may offer a direct protection against the development of atherosclerosis. Numerous studies have demonstrated that both the risk of coronary heart disease (CHD) in humans and the severity of experimental atherosclerosis in animals are inversely correlated with serum HDL cholesterol (HDL-C) concentrations (Russ et al., Am. J. Med., 11 (1951) 480-493; Gofman et al, Circulation, 34 (1966) 679-697; Miller and Miller, Lancet, 1 (1975) 16-19; Gordon et al., Circulation, 79 (1989) 8-15; Stampfer et al., N. Engl. J. Med., 325 (1991) 373-381; Badimon et al., Lab. Invest., 60 (1989) 455-461). Atherosclerosis is the process of accumulation of cholesterol within the arterial wall which results in the occlusion, or stenosis, of coronary and cerebral arterial vessels and subsequent myocardial infarction and stroke. Angiographical studies have shown that elevated levels of some HDL particles in humans appears to be correlated to a decreased number of sites of stenosis in the coronary arteries of humans (Miller et al., Br. Med. J., 282 (1981) 1741-1744).

There are several mechanisms by which HDL may protect against the progression of atherosclerosis. Studies in vitro have shown that HDL is capable of removing cholesterol from cells (Picardo et al., Arteriosclerosis, 6 (1986) 434-441). Data of this nature suggest that one antiatherogenic property of HDL may lie in its ability to deplete tissues of excess free cholesterol and eventually lead to the delivery of this cholesterol to the liver (Glomset, J. Lipid Res., 9 (1968) 155-167). This has been supported by experiments showing efficient transfer of cholesterol from HDL to the liver (Glass et al., Circulation, 66 (Suppl. II) (1982) 102; MacKinnon et al., J. Biol. Chem., 261 (1986) 2548-2552). In addition, HDL may serve as a reservoir in the circulation for apoproteins necessary for the rapid metabolism of triglyceride-rich lipoproteins (Grow and Fried, J.

Biol. Chem., 253 (1978) 1834-1841; Lagocki and Scanu, J. Biol. Chem., 255 (1980) 3701-3706; Schaefer et al., J. Lipid Res., 23 (1982) 1259-1273). Accordingly, agents which increase HDL cholesterol concentrations are useful as anti-atherosclerotic agents, particularly in the treatment of dyslipoproteinemias and coronary heart disease.

BRIEF DESCRIPTION OF THE INVENTION

The compounds of this invention which elevate plasma levels of HDL cholesterol have the formula



wherein R^1, R^2, and R^3 are independently hydrogen, C_1-C_{10} alkyl, or -$(CH_2)_{0-6}Ar^1$ where Ar^1 is phenyl, furanyl, pyridinyl or thienyl, and Ar^1 is optionally substituted by halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, trifluoromethyl, C_1-C_6 alkoxycarbonyl, -CO_2H or OH;

and Ar is phenyl, naphthyl, furanyl, pyridinyl or thienyl optionally substituted by halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, trifluoromethyl, C_1-C_6 alkoxycarbonyl, -CO_2H or OH.

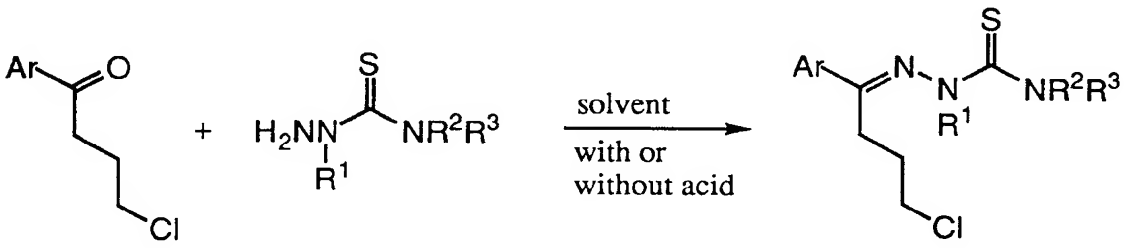
Compounds where Ar is phenyl, R^1 is hydrogen and one of R^2 and R^3 is methyl or phenyl and the other is hydrogen are known (S. Tomita *et al.*, J. Heterocyclic Chem., 27, 707 (1990)). A genus of nematocidal compounds disclosed in German patent 3,624,349 encompasses the invention compounds of the above formula when R^2 and R^3 are both hydrogen, but does not give any specific example of a thiosemicarbazide of a haloalkyl aryl ketone.

The compounds are tested *in vivo* in rats fed cholesterol-augmented rodent chow for 8 days according to the test protocol and blood from the rats analyzed for HDL cholesterol.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are conveniently prepared by the route shown in Scheme I. Specific examples are given in the Experimental Section. These examples are for illustrative purposes only and are not to be construed as limiting to this disclosure in any way. Those skilled in the art will be aware of other methods of preparing compounds of this invention. The starting materials or intermediates are available commercially or can be prepared by standard literature procedures.

Scheme I



Experimental

Example 1

2-(4-Chloro-1-phenyl-butylidene)-N-methyl-hydrazinecarbothioamide

A mixture of 4-chlorobutyrophenone (7.6 mL, 48 mmol) and 4-methylthiosemicarbazide (5.0 g, 48 mmol) in 300 mL of ethanol under a nitrogen atmosphere was warmed to dissolve all the solids and then allowed to stir at room temperature overnight. The solvent was removed under reduced pressure to give 13.0 g of a light yellow solid. Recrystallization of the solid form ethanol gave 7.25 g (57%) of the title compound as a white solid, mp 94-96 °C.

Elemental Analysis for $C_{12}H_{16}ClN_3S$

Calc'd: C, 53.42; H, 5.98; N, 15.58

Found: C, 53.38; H, 5.85; N, 15.60

Example 2

2-[4-Chloro-1-(pyridin-3-yl)-butylidene]-N-methyl-hydrazinecarbothioamide

A mixture of 4-chloro-1-(3-pyridinyl)-1-butanone (4.4 g, 24 mmol) and 4-methylthiosemicarbazide (2.5 g, 24 mmol) in 150 mL of ethanol under a nitrogen atmosphere was warmed to dissolve all the solids and then allowed to stir at room temperature overnight. By TLC the reaction was not complete. The reaction was then heated at 70 °C for 5 hours and overnight at room temperature. The solvent was removed under reduced pressure to give 7.29 g of a yellow oil. Purification of this oil on 700 g of silica gel (230-400 mesh) using 50-70% EtOAc-hexane as the eluent gave 4.14 g (64%) of the title compound as a white solid, mp 100-102 °C.

Elemental Analysis for $C_{11}H_{15}ClN_4S$

Calc'd: C, 48.79; H, 5.58; N, 20.69

Found: C, 48.57; H, 5.61; N, 20.75

Example 3

2-(4-Chloro-1-phenyl-butylidene)-N,N-dimethyl-hydrazinecarbothioamide

A mixture of 4-chlorobutyrophenone (13.1 mL, 81 mmol) and 4,4-dimethyl-3-thiosemicarbazide (9.7 g, 81 mmol) in 400 mL of ethanol under a nitrogen atmosphere was warmed to dissolve all the solids and then allowed to stir overnight at room temperature. The solid present was removed by filtration to give 2.17 g of a yellow solid. Chromatography of this solid on 200 g of silica gel (230-400 mesh) using 10% EtOAc-hexane as the eluent gave 765 mg of the title compound as a yellow solid. The original filtrate from the above solid was concentrated under vacuum to give an additional 20.8 g of a yellow solid. Chromatography of this solid as before using 1 kg of silica gel (230-400 mesh) gave 7.51 g of a yellow solid. Recrystallization of this solid from isopropyl alcohol gave 4.33 g of the title compound as a yellow solid. Total yield from the two fractions was 35%, mp 109-111°C.

Elemental Analysis for $C_{13}H_{18}ClN_3S$

Calc'd: C, 55.01; H, 6.39; N, 14.80

Found: C, 54.94; H, 6.42; N, 14.71.

Example 4

2-[1-Phenyl-4-chloro-butylidene]-N-[2-(pyridin-2-yl)ethyl]-hydrazinecarbothioamide

A mixture of 4-chlorobutyrophenone (8.5 mL, 53 mmol) and 4-(2-(2-pyridyl)ethyl)-3-thiosemicarbazide (9.5 g, 48 mmol) in 400 mL of ethanol was heated under a nitrogen atmosphere to 75 °C and then at that temperature for 24 hours (overnight). The solvent was removed under reduced pressure to give 20.3 g of a yellow oil. This oil was triturated with EtOAc to separate the desired product from the thiosemicarbazide. The ethyl acetate was removed under reduced pressure and the residue chromatographed on 1 kg of silica gel (230-400 mesh) using 10-20% EtOAc-hexane as the eluent. The material collected (2.86 g, yellow solid) was recrystallized from isopropyl alcohol to give 2.30 g (13%) of the title compound as an off-white solid, mp 126-129 °C.

Elemental Analysis for $C_{18}H_{21}N_4SCl \cdot 0.04\ C_3H_8O$

Calc'd: C, 59.90; H, 5.92; N, 15.12

Found: C, 60.14; H, 6.13; N, 15.42

Example 5

2-(4-Chloro-1-phenyl-butylidene)-N-hexyl-hydrazinecarbothioamide

A mixture of 4-chlorobutyrophenone (9.2 mL, 57 mmol) and 4-hexyl-3-thiosemicarbazide (10.0 g, 57 mmol) in 350 mL of ethanol was warmed under a nitrogen atmosphere to dissolve all the solids and then the reaction stirred at room temperature for 72 hours. The solvent was removed under reduced pressure to give 20.0 g of a yellow solid. Chromatography of this solid on 1 kg of silica gel (230-400 mesh) using 10-20% EtOAc-hexane as the eluent gave 16.8 g (87%) of the title compound as a light yellow solid, mp 42-44 °C.

Elemental Analysis for $C_{17}H_{26}ClN_3S$

Calc'd: C, 60.07; H, 7.71; N, 12.36

Found: C, 60.09; H, 7.83; N, 12.14

Example 6

2-(4-Chloro-1-phenyl-butylidene)-N-phenyl-hydrazinecarbothioamide

A mixture of 4-chlorobutyrophenone (6.7 mL, 42 mmol) and 4-phenyl-3-thiosemicarbazide (7.0 g, 42 mmol) in 500 mL of ethanol was warmed under a nitrogen atmosphere to dissolve all the solids and then the reaction stirred at room temperature for four days. The solid formed was collected by filtration and dried under reduced pressure to give 8.73 g of a white solid.. Recrystallization of the solid from ethanol gave 7.99 g (57%) of the title compound as a white solid, mp 107-109 °C.

Elemental Analysis for $C_{17}H_{18}N_3SCl$

Calc'd: C, 61.53; H, 5.47; N, 12.66

Found: C, 61.36; H, 5.42; N, 12.64

Example 7

2-(4-Chloro-1-phenyl-butylidene)-hydrazinecarbothioamide

Thiosemicarbazide (9.11 g, 0.1 mol) was added under nitrogen to a solution of 4-chlorobutyrophenone (16 mL, 0.1 mol) in 350 mL of methanol plus 27 mL of 1 N HCl plus 25 mL of water. After approximately 30 minutes of stirring at room temperature, all of the solid had dissolved. The reaction was then stirred at room temperature for 24 hours (overnight). The solid that had formed was collected by filtration and dried under high vacuum to give 17.41 g (68%) of the title compound as a white solid, mp 128-130 °C.

Elemental Analysis for $C_{11}H_{14}ClN_3S$

Calc'd: C, 51.66; H, 5.52; N, 16.43

Found: C, 51.69; H, 5.51; N, 16.10

Example 8

2-[4-Chloro-1-(thiophen-2-yl)-butylidene]-hydrazinecarbothioamide

Thiosemicarbazide (9.11 g, 0.1 mol) was added under nitrogen to a solution 4-chloro-2'-butyrothienone (16.2 mL, 0.1 mol) in 350 mL of methanol plus 27 mL 1N HCl plus 25 mL of water. After stirring at room temperature for approximately 2 hours, all of

the solid had dissolved. The reaction was then stirred at room temperature for 24 hours (overnight). By TLC starting material remained. An additional 27 mL of 1N HCl was added and the reaction stirred at room temperature for 6 hours. The solid formed was removed by filtration and dried under high vacuum to give 14.87 g (57%) of the title compound as a brown solid, mp 120-122 °C.

Elemental Analysis for $C_9H_{12}ClN_3S_2$

Calc'd: C, 41.29; H, 4.62; N, 16.05

Found: C, 40.96; H, 4.40; N, 16.03

Example 9

2-[1-(4-Chloro-phenyl)-4-chloro-butylidene]-hydrazinecarbothioamide

Thiosemicarbazide (9.11 g, 0.1 mol) was added under nitrogen to a solution of 4,4'-dichlorobutyrophenone (21.7 g, 0.1 mol) in 350 mL of methanol plus 27 mL of 1N HCl plus 25 mL of water and the reaction stirred at room temperature for 21 hours (overnight). The solid was collected by filtration and dried to give 20.23 g of a white solid. Recrystallization of the solid from isopropyl alcohol gave 8.37 g (29%) of the title compound as a light yellow solid, mp 125-126 °C.

Elemental Analysis for $C_{11}H_{13}Cl_2N_3S$

Calc'd: C, 45.52; H, 4.52; N, 14.48

Found: C, 45.59; H, 4.41; N, 14.40

Example 10

2-[1-(4-Methyl-phenyl)-4-chloro-butylidene]-hydrazinecarbothioamide

Thiosemicarbazide (6.84g, 75 mmol) was added under nitrogen to a solution of 4-chloro-4'-methylbutyrophenone (10.0g, 50 mmol) in 175 mL of methanol plus 13.5 mL of 1 N HCl plus 12.5 mL of water and the reaction stirred at room temperature overnight. The solid formed was collected by filtration and dissolved in methylene chloride. The organic solution was washed multiple times with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 10.15g of an off-white solid. Recrystallization of the solid from isopropyl alcohol gave 8.65g (64 %) of the title compound as an off-white solid, mp133-135°C.

Elemental Analysis for $C_{12}H_{16}ClN_3S$

Calc'd: C, 53.42; H, 5.98; N, 15.58

Found: C, 53.39; H, 6.08; N, 15.60

Example 11

2-[1-(4-Methoxy-phenyl)-4-chloro-butylidene]-hydrazinecarbothioamide

Thiosemicarbazide (6.4g, 70 mmol) was added under nitrogen to a solution of 4-chloro-4'-methoxybutyrophenone (10.0g, 47 mmol) in 150 mL of methanol plus 12.7 mL of 1 N HCl plus 11.8 mL of water and the reaction stirred for approximately three days (over the weekend). The solid formed was collected by filtration and dissolved in methylene chloride. The organic solution was washed multiple times with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a white solid. Recrystallization of the solid from isopropyl alcohol gave 8.46g (63%) of the title compound as a light yellow solid, mp 137-140°C.

Elemental Analysis for $C_{12}H_{16}ClN_3OS$

Calc'd: C, 50.43; H, 5.64; N, 14,70

Found: C, 50.14; H, 5.42; N, 14.41

Example 12

2-[1-(4-hydroxy-phenyl)-4-chloro-butylidene]-hydrazinecarbothioamide

Thiosemicarbazide (6.84g, 75 mmol) was added under nitrogen to a solution of 4-chloro-4'-hydroxybutyrophenone (10.0g, 50 mmol) in 175 mL of methanol plus 13.5 mL of 1 N HCl plus 12.5 mL of water and the reaction stirred room temperature for forty hours. The reaction was concentrated under reduced pressure to remove most of the methanol. The residue was partitioned between methylene chloride and water. The organic layer was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 8.33g of a white solid. Recrystallization of the solid from isopropyl alcohol gave 3.19g (21%) of the title compound as a light yellow solid, mp 126-129°C.

Elemental Analysis for $C_{11}H_{14}ClN_3OS \cdot 0.52\ C_3H_8O$

Calc'd: C, 49.79; H, 6.04; N, 13.87

Found C, 46.04; H, 4.77; N, 14.42

PHARMACOLOGY

In Vivo Assay: Male Sprague-Dawley rats weighing 200-225 g are housed two per cage and fed Purina Rodent Chow Special Mix 5001-S supplemented with 0.25% cholic acid and 1.0% cholesterol and water ad libitum for 8 days. Each test substance is administered to a group of six rats fed the same diet with the test diet mixed in as 0.005 - 0.1 % of the total diet. Body weight and food consumption are recorded prior to diet administration and at termination. Typical doses of the test substances are 5 - 100 mg/kg/day.

At termination, blood is collected from anesthetized rats and the serum is separated by centrifugation. Total serum cholesterol is assayed using the Sigma Diagnostics enzymatic kit for the determination of cholesterol, Procedure No. 352, modified for use with ninety-six well microtiter plates. After reconstitution with water the reagent contains 300 U/l cholesterol oxidase, 100 U/l horse radish peroxidase, 0.3 mmoles/l 4-aminoantipyrine and 30.0 mmoles/l p-hydroxybenzenesulfonate in a pH 6.5 buffer. In the reaction cholesterol is oxidized to produce hydrogen peroxide which is used to form a quinoneimine dye. The concentration of dye formed is measured spectrophotometrically by absorbance at 490 nm after incubation at 25 °C for 30 minutes. The concentration of cholesterol was determined for each serum sample relative to a commercial standard from Sigma.

HDL cholesterol concentrations in serum are determined by separation of lipoprotein classes by fast protein liquid chromatography (FPLC) by a modification of the method of Kieft et al., J. Lipid Res., 32 (1991) 859-866. 25 µl of serum is injected onto Superose 12 and Superose 6 (Pharmacia), in series, with a column buffer of 0.05 M Tris (2-amino-2-hydroxymethyl-1,3-propanediol) and 0.15 M sodium chloride at a flow rate of 0.5 ml/min. The eluted sample is mixed on line with Boehringer-Mannheim cholesterol reagent pumped at 0.2 ml/min. The combined eluents are mixed and incubated on line through a knitted coil (Applied Biosciences) maintained at a temperature of 45° C. The eluent is monitored by measuring absorbance at 490 nm and gives a continuous absorbance signal proportional to the cholesterol concentration. The relative concentration of each lipoprotein class is calculated as the per cent of total absorbance. HDL cholesterol concentration, in serum, is calculated as the per cent of total cholesterol as determined by FPLC multiplied by the total serum cholesterol concentration. The test results are presented in Table I.

TABLE I

Cholesterol Fed Rat

Example	% Increase in HDL (Dose)
Example 1	22% (95 mg/kg)
Example 2	N.T.
Example 3	43.5% (90 mg/kg)
Example 4	33.1% (100 mg/kg)
Example 5	31.4% (100 mg/kg)
Example 6	15.1% (100 mg/kg)
Example 7	204% (100 mg/kg)
Example 8	112.5% (100 mg/kg)
Example 9	67.5% (100 mg/kg)
Example 10	26.8% (100 mg/kg)
Example 11	31.3% (100 mg/kg)
Example 12	88.6% (111 mg/kg)

PHARMACEUTICAL COMPOSITION

Compounds of this invention may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid.

Applicable solid carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties In suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such a solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferable sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

The compounds of this invention may be administered rectally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semi-solid emulsions of either the oil in water or water in oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

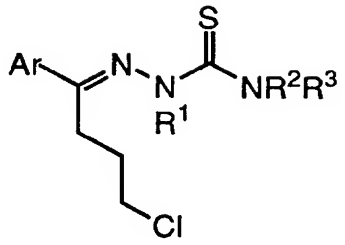
The dosage to be used in the treatment of a specific patient suffering from high density lipoprotein insufficiency must be subjectively determined by the attending physician. The variables involved include the severity of the dysfunction, and the size,

age, and response pattern of the patient.. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages for oral or parenteral administration will be determined by the administering physician based on experience with the individual subject treated and standard medical principles.

Preferably the pharmaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example packed powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

What is claimed is:

(1) A compound of the formula



wherein R^1, R^2, and R^3 are independently hydrogen, C_1-C_{10} alkyl, or -$(CH_2)_{0-6}Ar^1$ where Ar^1 is phenyl, furanyl, pyridinyl or thienyl, or Ar^1 is optionally substituted by halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, trifluoromethyl, C_1-C_6 alkoxycarbonyl, -CO_2H or OH;

and Ar is phenyl, naphthyl, furanyl, pyridinyl or thienyl optionally substituted by halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, trifluoromethyl, C_1-C_6 alkoxycarbonyl, -CO_2H or OH;

with the proviso that when Ar is phenyl and R^1 is hydrogen, and one of R^2 and R^3 is hydrogen, then the other or R^2 and R^3 cannot be methyl or phenyl.

(2) A compound according to claim 1 which is 2-(4-chloro-1-phenyl-butylidene)-hydrazinecarbothioamide.

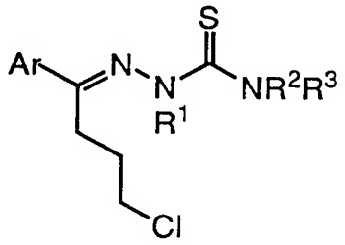
(3) A compound according to claim 1 which is 2-[4-chloro-1-(thiophen-2-yl)-butylidene]-hydrazinecarbothioamide.

(4) A compound according to claim 1 which is 2-[1-(4-chloro-phenyl)-4-chloro-butylidene]-hydrazinecarbothioamide.

(5) A compound according to claim 1 which is selected from
2-[4-chloro-1-(pyridin-3-yl)-butylidene]-N-methyl-hydrazinecarbothioamide,
2-(4-chloro-1-phenyl-butylidene)-N,N-dimethyl-hydrazinecarbothioamide,
2-[1-phenyl-4-chloro-butylidene]-N-[2-(pyridin-2-yl)ethyl]-hydrazinecarbothioamide,

2-(4-chloro-1-phenyl-butylidene)-N-hexyl-hydrazinecarbothioamide,
2-[1-(4-methyl-phenyl)-4-chloro-butylidene]-hydrazinecarbothioamide,
2-[1-(4-methoxy-phenyl)-4-chloro-butylidene]-hydrazinecarbothioamide, and
2-[1-(4-hydroxy-phenyl)-4-chloro-butylidene]-hydrazinecarbothioamide.

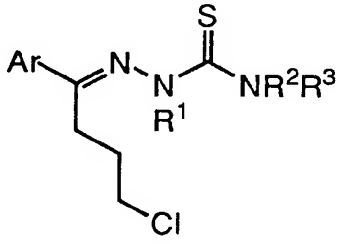
(6) A method of treating atherosclerosis in mammals which comprises administration to a mammal having atherosclerosis a therapeutically effective amount of a compound of the formula



wherein R^1, R^2, and R^3 are independently hydrogen, C_1-C_{10} alkyl, or -$(CH_2)_{0-6}Ar^1$ where Ar^1 is phenyl, furanyl, pyridinyl or thienyl, or Ar^1 is optionally substituted by halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, trifluoromethyl, C_1-C_6 alkoxycarbonyl, -CO_2H or OH;

and Ar is phenyl, naphthyl, furanyl, pyridinyl or thienyl optionally substituted by halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, trifluoromethyl, C_1-C_6 alkoxycarbonyl, -CO_2H or OH.

(7) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula



wherein R^1, R^2, and R^3 are independently hydrogen, C_1-C_{10} alkyl, or -$(CH_2)_{0-6}Ar^1$ where Ar^1 is phenyl, pyranyl, pyridinyl or thienyl, or Ar^1 is

optionally substituted by halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, trifluoromethyl, C_1-C_6 alkoxycarbonyl, -CO_2H or OH;

and Ar is phenyl, naphthyl, furanyl, pyridinyl or thienyl optionally substituted by halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, trifluoromethyl, C_1-C_6 alkoxycarbonyl, -CO_2H or OH.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 98/10461

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C337/08 A61K31/325

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J.M. CHAPMAN JR: LIPIDS, vol. 25, no. 7, 1990, pages 391-397, XP002080248 see table 2, compounds Ib, IIb, IIIb, IVb, IVf, IVj, IVn ---	1,6,7
A	Y. TOMITA ET AL: J. HETEROCYCL. CHEM., vol. 27, no. 3, 1990, pages 707-710, XP002081678 cited in the application see page 708, scheme 4, formula 11 ---	1
A	DE 36 24 349 A (SCHERING AG) 28 January 1988 cited in the application see claims 1,2 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
21 October 1998	11/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 10461

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 6
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/US 98/10461

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 3624349 A	28-01-1988	AU 604032 B	06-12-1990
		AU 7573087 A	21-01-1988
		DD 261303 A	26-10-1988
		DK 373787 A	18-01-1988
		EP 0254461 A	27-01-1988
		FI 873002 A	18-01-1988
		JP 63093761 A	25-04-1988
		US 4983755 A	08-01-1991